CERTIFICATE OF MAILING
37 C.F.R. § 1.8

I hereby certify that this correspondence is being deposited with the U.S. Postal Service with sufficient postage as First Class Mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Arlington, VA 22313-1450, on the date below:

January 12, 2005
Date

Shelley P.M. Fussey

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Philip E. Thorpe, Sophia Ran and
Rolf A. Brekken (As Amended)

Serial No.: 09/351,149

Filed: July 12, 1999

For: Cancer Treatment Kits Comprising Therapeutic Conjugates that Bind to Aminophospholipids

Group Art Unit: 1617

Examiner: Sharareh, S.

Atty. Dkt. No.: 3999.002383

SUBMISSION OF EARLIER DECLARATION INTO PRESENT APPLICATION; COPY OF DECLARATION OF PHILIP E. THORPE, SOPHIA RAN AND ROLF A. BREKKEN UNDER 37 C.F.R. § 1.131

Commissioner for Patents
P.O. Box 1450
Arlington, VA 22313-1450

Sir:

Applicants respectfully submit the attached Declaration for formal consideration in the above-referenced application. Original versions of the attached Declaration and accompanying exhibits were submitted in application Serial No. 09/351,598, now U.S. Patent No. 6,818,213.

Respectfully submitted,
Williams, Morgan & Amerson, P.C.
Customer No. 23720

Shelley P.M. Fussey, Ph.D.
Reg. No. 39,458
Agent for Applicant

10333 Richmond, Suite 1100
Houston, Texas, 77042
(713) 934-4079
Date: January 12, 2005

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Philip E. Thorpe, Sophia Ran and Rolf A. Brekken (As Amended)	§	
	§	Group Art Unit: 1642
Serial No.: 09/351,598	§	
	§	Examiner: Bansal, G.
Filed: July 12, 1999	§	
	§	Atty. Dkt.: 3999.002382
For: CANCER TREATMENT COMPOSITIONS COMPRISING THERAPEUTIC CONJUGATES THAT BIND TO AMINOPHOSPHOLIPIDS	§	

CERTIFICATE OF MAILING
37 C.F.R. § 1.8

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as First Class Mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on the date below:

May 10, 2002
Date

Shelley P. M. Fussey

DECLARATION OF PHILIP E. THORPE, SOPHIA RAN AND ROLF A. BREKKEN UNDER 37 C.F.R. § 1.131

Assistant Commissioner for Patents
Washington, D.C. 20231

WE, PHILIP E. THORPE, SOPHIA RAN AND ROLF A. BREKKEN, HEREBY DECLARE AS FOLLOWS:

1. We are co-inventors of the subject matter disclosed and claimed in the captioned patent application.

2. I, Philip E. Thorpe, am Professor of Pharmacology and hold the Serena S. Simmons Distinguished Chair in Immunopharmacology at the Simmons Cancer Center, The University of Texas Southwestern Medical Center at Dallas, Dallas, Texas. I am a British subject and a

permanent resident in the United States. I live at 5311 Nakoma Drive, Dallas, Texas, 75209, U.S.A.

3. I, Sophia Ran, am an Assistant Professor at the Simmons Cancer Center, The University of Texas Southwestern Medical Center at Dallas, Dallas, Texas. I am a citizen of Israel and a permanent resident in the United States. I live at 5840 Spring Valley Road, #1612, Dallas, Texas, 75240, U.S.A.

4. I, Rolf A. Brekken, am a Postdoctoral Fellow at The Hope Heart Institute, Seattle, Washington. I am a U.S. citizen and live at 14304 25th Ave NE, Seattle, Washington, 98125, U.S.A. Immediately prior to my present employment, I worked in the laboratory of Philip E. Thorpe at The University of Texas Southwestern Medical Center at Dallas ("UT Southwestern"). In June of this year, I will be returning to employment at UT Southwestern.

5. We have reviewed the Official Action dated April 08, 2002 issued by the U.S. Patent and Trademark Office (P.T.O.), the government agency charged with assessing the patentability of the captioned patent application. We have also reviewed the English translation of the document by Kuriyama, PCT publication WO 98/29453, cited in the Official Action.

6. We understand that the P.T.O. has taken the position that the claims in the captioned patent application would be obvious to one of skill in this field of study in light of the Kuriyama, WO 98/29453 document.

7. According to the cover page of the document itself, we understand that WO 98/29453 was published on July 09, 1998.

8. We are providing the present declaration and attached documentary evidence to demonstrate that the invention claimed in the captioned patent application was made in the United States prior to July 09, 1998, *i.e.*, prior to the publication date of the WO 98/29453 document.

9. Evidence of the fact that the invention claimed in the captioned patent application was made in the United States prior to July 09, 1998 is shown in the attached Exhibits and described in the following paragraphs. The studies described in the following paragraphs were conducted in Dallas, Texas, in the United States.

10. The captioned patent application claims binding ligands, compositions and pharmaceutical compositions thereof, in which the binding ligands comprise at least a first targeting agent that binds to an aminophospholipid, operatively attached to at least a first therapeutic agent. As we discovered that aminophospholipids are expressed on the luminal surface of blood vessels within a vascularized tumor, the binding ligands, compositions and pharmaceuticals are useful in targeting therapeutic agents to tumor blood vessels to achieve anti-tumor effects.

11. The claimed binding ligands include those with targeting agents that bind to the aminophospholipid, phosphatidylserine (PS); and those with targeting agents that bind to the

aminophospholipid, phosphatidylethanolamine (PE). The targeting agents may be anti-aminophospholipid antibodies, such as anti-PS or anti-PE antibodies; or aminophospholipid binding proteins, such as annexins, *e.g.*, annexin V, or a kininogen.

12. Exemplary evidence of the concept of certain aspects of the claimed invention is provided in **Exhibit A**, a copy of correspondence dated prior to July 09, 1998 from Philip E. Thorpe and Rolf A. Brekken to Shelley P.M. Fussey, then employed at the law firm of Arnold, White & Durkee. The correspondence describes those aspects of the invention for targeting therapeutic agents, such as drugs or coagulants, to tumor blood vessels for tumor therapy or imaging using annexins, such as annexin V, which bind to phosphatidylserine.

13. The correspondence of **Exhibit A**, dated prior to July 09, 1998, describes the rationale for using annexins to home selectively to tumor vascular endothelium after systemic administration. This correspondence describes making chemical constructs between annexins and drugs or coagulants, as well as fusing genes encoding annexins and cytotoxic proteins (*e.g.*, diphtheria toxin or ricin) or coagulants (*e.g.*, tissue factor, factor Xa, thrombin). It is also explained that radionuclides or imaging agents can be attached to annexins to produce reagents for imaging tumor vasculature.

14. Evidence of the generation of a binding ligand in which the targeting agent is annexin V and the therapeutic agent is the coagulant truncated tissue factor (tTF) is shown in **Exhibit B**, copies of laboratory notebook pages dated prior to July 09, 1998. The data of **Exhibit B** shows

results from construction and fractionation techniques, culminating in samples of purified annexin V-tTF shown on reducing and non-reducing gels.

15. The use of an annexin V-tTF targeting agent-therapeutic agent construct to successfully treat tumors *in vivo* is shown in **Exhibit C**, which represents the data from studies conducted prior to July 09, 1998.

16. In the studies depicted in **Exhibit C**, an annexin V-tTF conjugate was administered to nu/nu mice with solid tumors. The tumors were formed from human HT29 colorectal carcinoma cells that gave rise to tumors of at least about 1.2 cm^3. The annexin V-tTF construct was administered intravenously and allowed to circulate for 24 hours. Saline-treated mice were separately maintained as control animals. After the one day treatment period, the mice were sacrificed and exsanguinated and the tumors and major organs were harvested for analysis.

17. **Exhibit C**, based on studies conducted prior to July 09, 1998, shows that the annexin V-tTF conjugate induced specific tumor blood vessel coagulation in HT29 tumor bearing mice. Approximately 55% of the tumor blood vessels in the annexin V-tTF conjugate treated animals were thrombosed following a single injection. In contrast, only 12% of the tumor vasculature in the control animals showed evidence of thrombosis.

18. Exemplary evidence of the concept of those aspects of the claimed invention in which the targeting agent of the binding ligand is an antibody is shown in **Exhibit D**, a copy of correspondence dated prior to July 09, 1998 from Philip E. Thorpe to Dr. Neal S. Rote of Wright

State University. This correspondence requests samples of anti-PS antibodies from Dr. Rote, so that Drs. Thorpe and Ran can proceed with a fuller study after the inventors' finding that phosphatidylserine is a marker of tumor vascular endothelium. The anti-cardiolipin antibodies requested are for use as a control in the planned studies.

19. The correspondence of **Exhibit D**, dated prior to July 09, 1998, describes the preparation and testing of binding ligands in the form of anti-PS antibodies linked to tissue factor. These are described as anti-PS-tissue factor "coaguligands". We employ the term "coaguligand" to refer to a binding ligand in which a targeting agent that binds to a marker of tumor vasculature is linked to a coagulant. Thus, an "anti-PS-tissue factor coaguligand", as described in this correspondence, is an antibody directed against phosphatidylserine linked to a coagulant based on the tissue factor molecule. The correspondence explains that antibody (IgM) purification and conjugation will be performed by Drs. Thorpe and Ran.

20. Evidence of the shipment of antibodies against phosphatidylserine from Dr. Neal Rote to Drs. Thorpe and Ran at a date prior to July 09, 1998 is shown in the correspondence from Dr. Thorpe to Mr. Richard U. Rodriguez, of the Office of Legal Affairs and Technology Transfer at UT Southwestern, also dated prior to July 09 (**Exhibit E**).

21. Additional evidence concerning the existence of this invention prior to July 09, 1998 is shown in **Exhibit F**, a copy of correspondence from Mr. Louis T. Pirkey of the law firm of Arnold, White & Durkee to Mr. Ray Wheatley of the Office of Legal Affairs & Technology Transfer at UT Southwestern. This correspondence, dated prior to July 09, 1998, formally

acknowledges receipt of an invention disclosure entitled "Cancer Treatment Using Antibody Conjugates to Phosphatidylserine" and lists the inventors as "Thorpe and Ran". The correspondence includes the particular file code "UTSD:556", which still forms the basis of UT Southwestern's file reference for the captioned application (UTSD:556--1), and confirms Mr. Wheatley's request that the matter be handled by Shelley Fussey, then employed at the law firm of Arnold, White & Durkee.

22. **Exhibit G** is a copy of additional correspondence dated prior to July 09, 1998 from Mr. Wheatley of UT Southwestern to Shelley Fussey. The correspondence refers to "our phone conference today with Dr. Thorpe", *i.e.*, a telephone conference held prior to July 09, 1998, and authorizes the filing of two provisional patent applications. The correspondence of **Exhibit G** particularly itemizes the inclusion of "coaguligand" effector molecules and "other" effector molecules, which were included in the claims of the provisional application that was filed (see below).

23. We, Philip E. Thorpe and Sophia Ran, recall that a lengthy and detailed draft of the provisional application was prepared by Shelley Fussey and forwarded for our review prior to July 09, 1998. I, Philip E. Thorpe, particularly recall meeting with Shelley Fussey, who traveled to Dallas to discuss the near-to-final draft of the application prior to July 09, 1998, and I have recorded this meeting on my calendar for the date in question.

24. From the time of our documented development of the invention prior to July 09, 1998, we worked diligently on various aspects of the invention in the United States up to and including

July 13, 1998, when the first U.S. provisional patent application directed to our invention was filed.

25. **Exhibit H** shows front page, claims and abstract of the first U.S. provisional patent application directed to our invention that was filed on July 13, 1998. The claims include targeting agents that bind to phosphatidylserine, as represented at least in claims 3, 6, 9, 12, 15, 18, 123, 131 and 145; claims in which the targeting agent is an anti-aminophospholipid antibody or antigen-binding fragment thereof, as represented at least in claims 19-41, 48, 75, 126, 132, 133, 143-147, 151 and 153; and claims in which the targeting agent is an aminophospholipid binding protein or an aminophospholipid-binding fragment thereof, as represented at least in claims 42-46 and 127-128, 134-136, 148, 149 and 152. As outlined in the correspondence of **Exhibit G**, the claims in this provisional application include "coaguligands", as represented at least in claims 59-67, 138, 139, 146 and 147, and "other" effector molecules, as represented at least in claims 51-58 and 137 (**Exhibit H**).

26. From a time prior to July 09, 1998, through July 13, 1998 to the present time, we have continued to work diligently on various aspects of the claimed invention in the United States.

27. We hereby declare that all statements made herein of our knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

5/8/02
Date

Philip E. Thorpe
Philip E. Thorpe

5/8/2002
Date

Sophia Ran
Sophia Ran

Date

Rolf A. Brekken

27. We hereby declare that all statements made herein of our knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date	Philip E. Thorpe
Date	Sophia Ran
5/7/02 Date	Rolf A. Brekken

A

SOUTHWESTERN
THE UNIVERSITY OF TEXAS
SOUTHWESTERN MEDICAL CENTER
AT DALLAS

Philip E. Thorpe, Ph.D.
Professor
The Serena S. Simmons Distinguished Chair
in Cancer Immunopharmacology

Department of Pharmacology
Nancy B. and Jake L. Hamon Center
for Therapeutic Oncology Research

Shelley P.M. Fussey, Ph.D.
Director of Molecular Scientific Resources
Arnold, White & Durkee
1900 One American Center
600 Congress Avenue
Austin, Tx 78701

Dear Shelley:

We would like to place on record the concept of an invention.

We envision a method for targeting drugs, coagulants or imaging agents to tumor blood vessels for tumor therapy or imaging. Annexins (e.g. annexin V) are a family of human proteins that bind with high affinity (Kd = 7nM) to phosphatidylserine, a simple phospholipid that becomes exposed on the surface of activated cells (platelets and nucleated cells) and on apoptotic or injured cells. Several factors known to be present in tumors lead us to expect that annexins would home selectively to tumor vascular endothelium after systemic administration. These factors include; i) activation of endothelial cells by cytokines released by tumor cells and infiltrating host cells; ii) death or apoptosis of endothelial cells in tumors due to oxygen starvation or physical compression; iii) apoptosis of endothelial cells in tumors due to vascular remodeling which is believed to involve endothelial cell death as well as endothelial cell migration and proliferation; iv) deposition of and activation of platelets on tumor vessels and binding of annexins to the bound platelets. None of these factors is likely to be as prominent in the vessels of normal tissues. If annexins localize selectively to tumor endothelium, it should be possible to make chemical constructs between annexins and drugs or coagulants. It should also be possible to fuse the genes encoding annexins and cytotoxic proteins (e.g. diphtheria toxin, ricin) or coagulant proteins (e.g. tissue factor, factor Xa, thrombin). Such agents might be useful for modulating or thrombosing tumor vasculature. Similarly, radionucleides or imaging agents might be attached to annexins to produce reagents for imaging tumor vasculature.

These concepts were conceived jointly by us without inventive input from other people.

Yours Sincerely,

Philip E Thorpe

P.E. Thorpe, Ph.D.
Professor of Pharmacology

R.A. Brekken, B.S.
Graduate Student

Making Annexin V — tTF.

Annexin V · 5 mg/ml in Hepes / NaCl pH 7.4

tTF. N-cys ER protection. 30%.

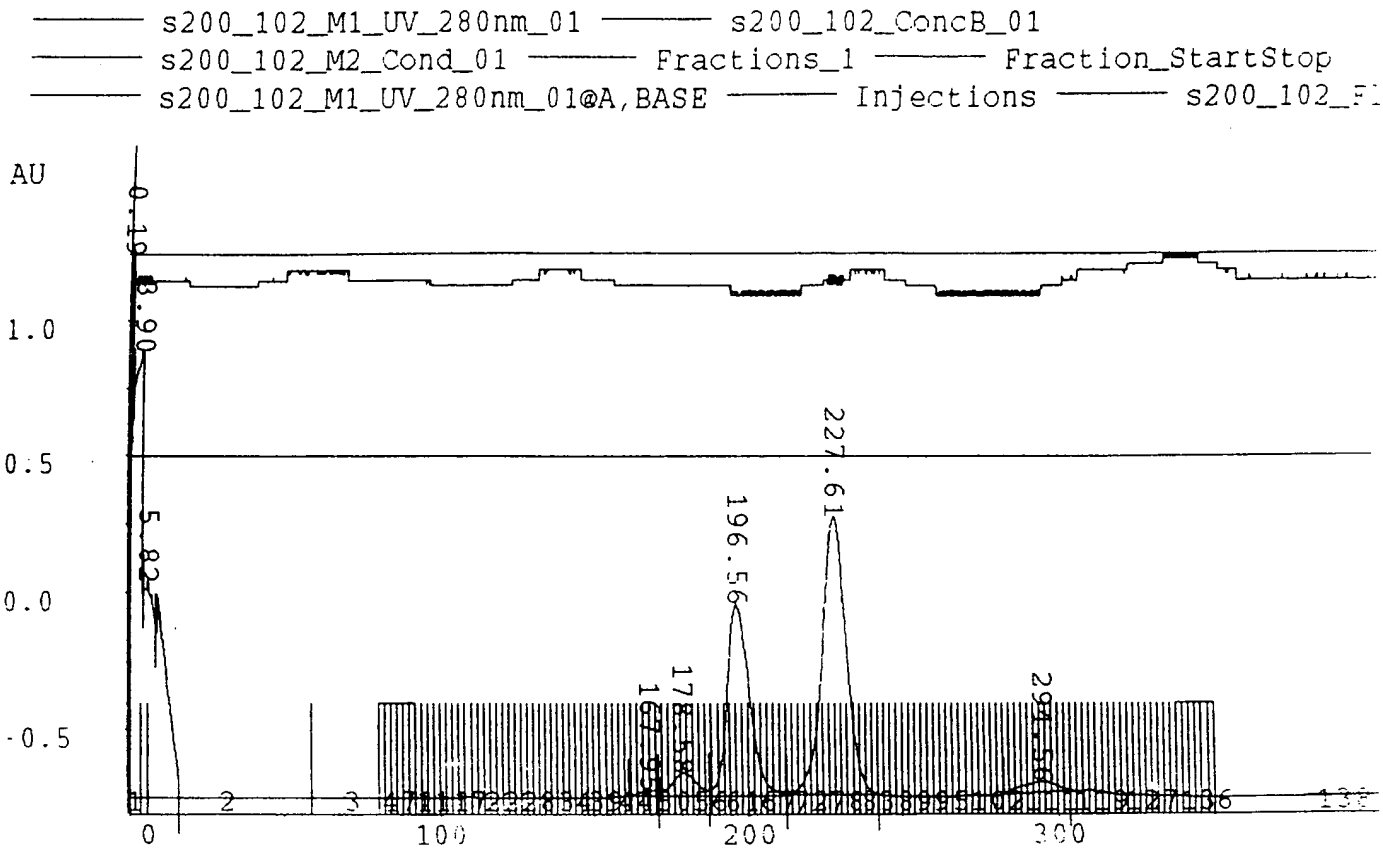
1. Derivatizing Annexin V w/ 2-IT at molar ratio: 15:1. give a ratio of. — SH / annexin V : 1.8:1

2. Collect fraction directly into tTF-ER.

1. Annexin V
2. tTF:ER
3. Marker
4. Annexin V
5. tTF. ER

1 2 3 4

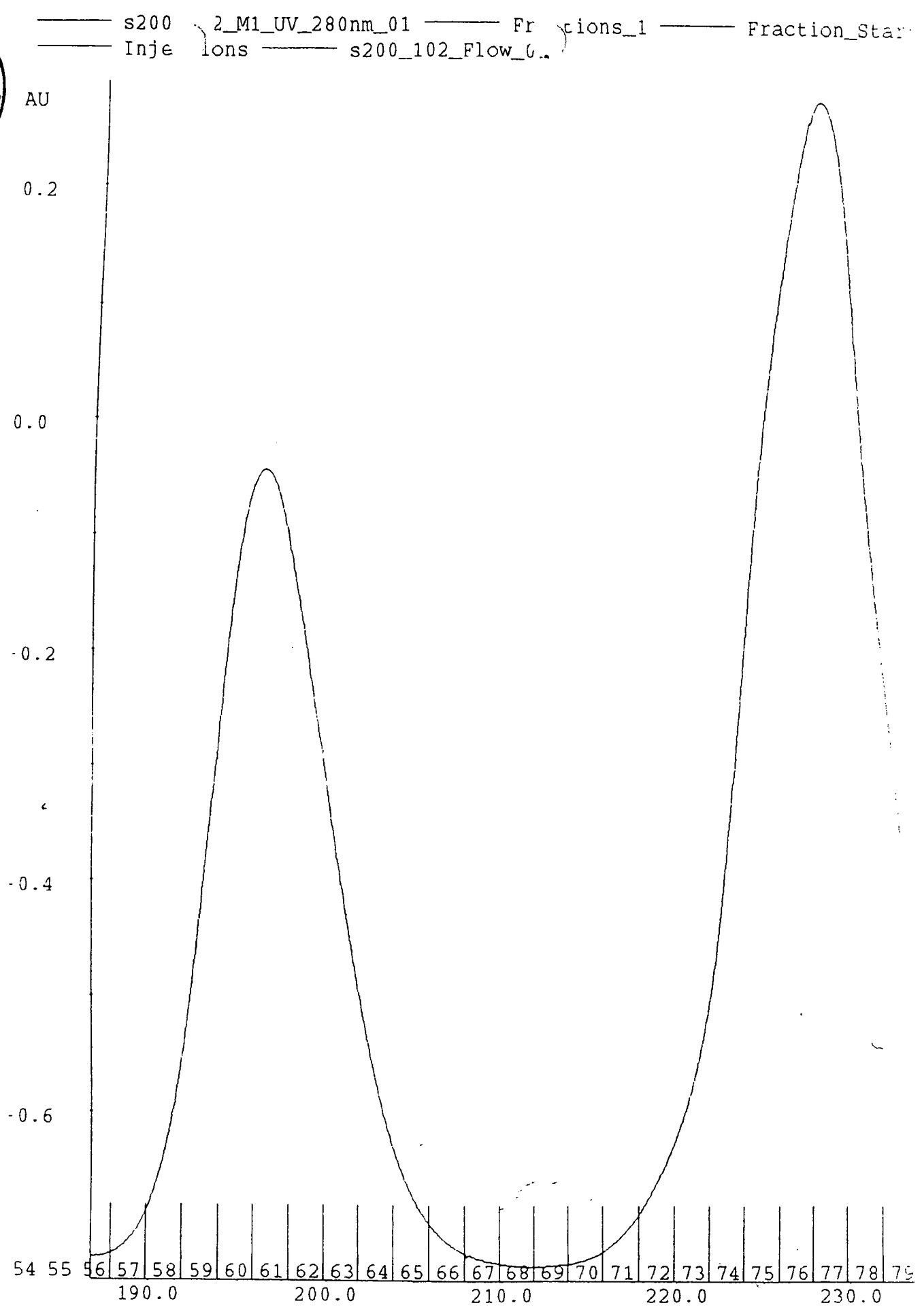
1. VEGF$_{165}$ KB's
2. "
3. conjugate before purifying
4.

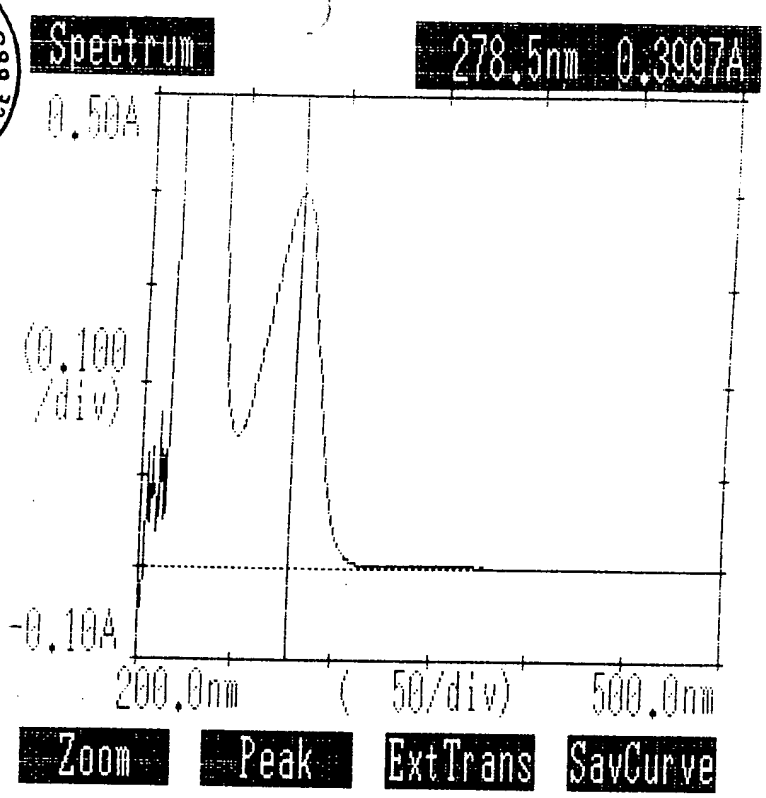


Peaktable-A: s200_102_M1_UV_280nm_01@A.PEAK

No	Ret ml	Peak start ml	Peak end ml	Width ml	Area AU*ml	Height AU
1	0.19	-0.13	0.58	0.77	1.0852	2.000
2	3.90	0.58	4.22	3.71	5.5338	1.638
3	5.82	4.22	8.45	4.29	3.0727	0.795
4	8.70	8.45	15.55	7.17	2.9492	0.744
5	167.95	161.17	170.90	9.79	0.1343	0.021
6	178.58	170.90	186.90	16.07	0.7785	0.085
7	196.56	186.90	212.12	25.28	5.9404	0.700
8	227.61	212.12	242.33	30.27	9.3462	1.017
9	294.56	282.14	303.52	21.44	0.5114	0.039

Total number of detected peaks = 9
Total area = 29.380488 AU*ml
Area in evaluated peaks = 29.351683 AU*ml
Ratio peak area / total area = 0.999020
Total peak width = 118.795270 ml





Combine fraction 65~58.

total vol 14 mls

1. purified Annexin V-TTF reduced gel.

2. purified Annexin V-TTF non-reduced gel

C

A. Design:

HT29 human colorectal carcinoma cells grown in tissue (1×10^7 cells) were injected subcutaneously into the right flank of 6-7 week old male nu/nu mice

↓

Allow tumors to grow to a volume of 1.2 cm^3 or more

↓

Inject 0.3 µg of annexinV-tTF (or as a control, 350 µl of saline) into mice intravenously

↓

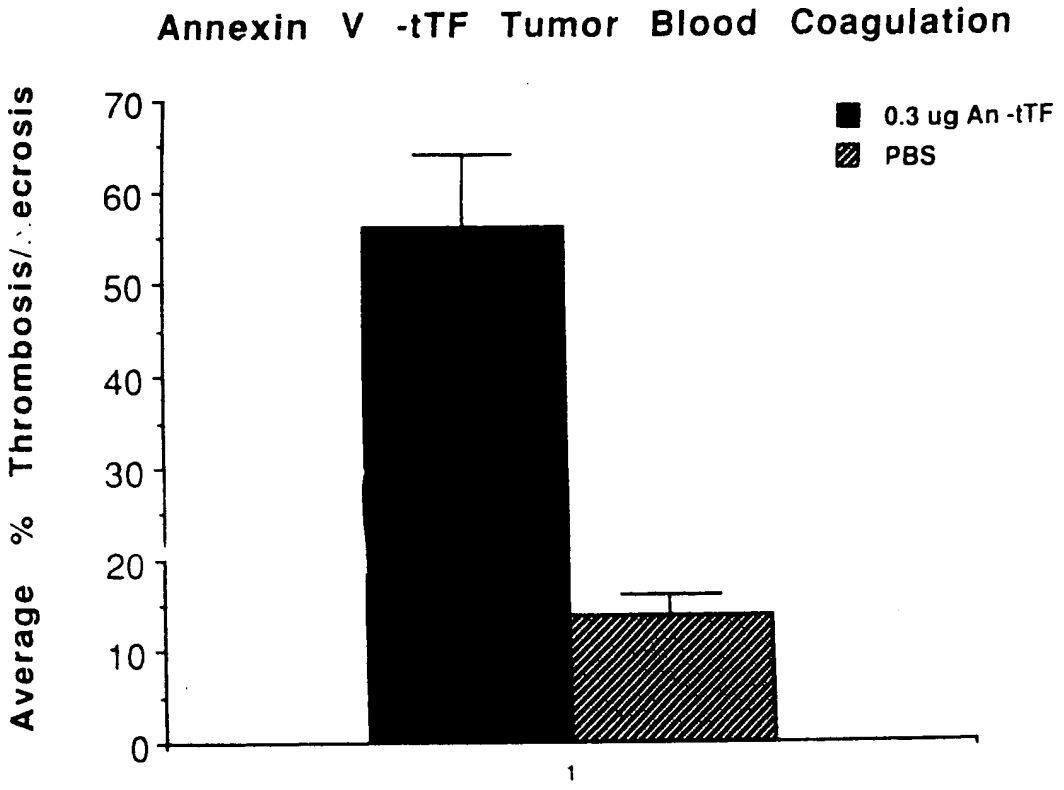
Sacrifice and exsanguinate animals 24 hours later

↓

Harvest tumors and all major organs and retain the samples for H & E staining

B. Results:

The attached Figure demonstrates that the annexinV-tTF conjugate induces specific tumor blood vessel coagulation in HT29 tumor bearing mice. Approximately 55% of the tumor blood vessels in the annexinV-tTF conjugate treated animals were thrombosed following a single injection. In contrast, only 12% of the tumor vasculature in the control animals showed evidence of thrombosis.



D

SOUTHWESTERN
THE UNIVERSITY OF TEXAS
SOUTHWESTERN MEDICAL CENTER
AT DALLAS

Philip E. Thorpe, Ph.D.
Professor
The Serena S. Simmons Distinguished Chair
in Cancer Immunopharmacology

Department of Pharmacology
Nancy B. and Jake L. Hamon Center
for Therapeutic Oncology Research

Dr. Neal S. Rote
Professor and Chairman
Department of Microbiology
and Immunology
Wright State University
002 Math & Micro. Science Bldg.
Dayton, OH 45435

Dear Neal:

We are very pleased you have agreed to collaborate on projects concerning PS expression on tumor vascular endothelium. We invite you to be a coauthor on primary manuscripts that emerge from these projects.

As I mentioned, Sophia Ran has found that PS is a marker of tumor vascular endothelium. Probably, PS becomes expressed as part of the switch from a fibrinolytic to a prothrombotic phenotype that is known to occur on tumor endothelium.

We would like to proceed to a fuller study of this work and would appreciate receiving from you 4 to 5 vials (8-10 ml total) of anti-PS and anti-cardiolipin hybridoma supernatants as soon as possible. We would also like to instigate a further project on preparing and testing anti-PS-tissue factor "coaguligands". For this we would need around 2 liters of culture supernatant from both the anti-PS and the anti-cardiolipin hybridomas. We will then do the IgM purification and conjugation, unless your lab is set up to do the purification for us. Obviously, producing the supernatants takes time and effort: if you need any help on this, please let me know.

These are exciting projects and we are enthusiastic to proceed with them.

Also, please send copies of papers describing the primary characterization of the specificity of your anti-PS and anti-cardiolipin antibodies.

I hope to see you in Maine before too long.

With my thanks and best wishes.

Yours sincerely,

Philip E. Thorpe, Ph.D.
Professor of Pharmacology

cc: Dr. Sophia Ran

E

SOUTHWESTERN
THE UNIVERSITY OF TEXAS
SOUTHWESTERN MEDICAL CENTER
AT DALLAS

Philip E. Thorpe, Ph.D.
Professor
The Serena S. Simmons Distinguished Chair
in Cancer Immunopharmacology

Department of Pharmacology
Nancy B. and Jake L. Hamon Center
for Therapeutic Oncology Research

Mr. Richard U. Rodriguez
Technology Analyst
Office of Legal Affairs and
Technology Transfer
UT Southwestern

RE: UTSD:549 — Immunotherapy of Cancer with Antibodies to a Marker of Tumor Vascular Endothelium

Dear Mr. Rodriguez:

The monoclonal antibodies, 35B9b against phosphatidylserine and D11A4 against cardiolipin, were sent to Dr. Sophia Ran and myself by Dr. Neal Rote of Wright State University, Ohio, without any commercial obligations or material transfer agreement. We agreed to include Dr. Rote as a coauthor on primary manuscripts but this is the only obligation of which we are aware.

The first shipment of antibodies was made on . The idea of using the antibodies for immunotherapy that is the subject of the above invention came from the surprising observation by Dr. Ran that administration of Dr. Rote's anti-phosphatidylserine antibody to tumor bearing mice caused selective thrombosis of tumor blood vessels.

Yours sincerely,

Philip Thorpe

Philip E. Thorpe, Ph.D.
Professor of Pharmacology

cc: Dr. Sophia Ran
Mr. Ray Wheatley
Ms. Shelley Fussey

F

ARNOLD, WHITE & DURKEE
A PROFESSIONAL CORPORATION
Attorneys at Law

1900 ONE AMERICAN CENTER
600 CONGRESS AVENUE
AUSTIN, TX 78701-3248
TELEPHONE (512) 418-3000
FACSIMILE (512) 474-7577

...O BERING DRIVE, SUITE 400
HOUSTON, TX 77057-2198
TELEPHONE (713) 787-1400
FACSIMILE (713) 789-2679

155 LINFIELD DRIVE
MENLO PARK, CA 94025-3741
TELEPHONE (415) 614-4500
FACSIMILE (415) 614-4599

4850 FIRST BANK PLACE
601 SECOND AVE. SOUTH
MINNEAPOLIS, MN 55402-4320
TELEPHONE (612) 321-2800
FACSIMILE (612) 321-9600

800 QUAKER TOWER
321 NORTH CLARK STREET
CHICAGO, IL 60610-4714
TELEPHONE (312) 744-0090
FACSIMILE (312) 755-4489

2001 JEFFERSON DAVIS HIGHWAY
SUITE 401
ARLINGTON, VA 22202-3604
TELEPHONE (703) 415-1720
FACSIMILE (703) 415-1728

LOUIS T. PIRKEY
(512) 418-3001

UTSD:556

Ray Wheatley, M.S.
Director of Technology Transfer
Office of Legal Affairs & Technology Transfer
Technology Transfer Office
UT Southwestern Medical Center at Dallas
5323 Harry Hines Boulevard
Dallas, TX 75235-9094

Re: ***Invention Disclosure Entitled:*** *"Cancer Treatment Using Antibody Conjugates to Phosphatidylserine" - Thorpe and Ran (UTSMC/DAL:556)*

Dear Ray:

This will acknowledge your ; e-mail and authorization to perform a patentability search and provide an oral opinion on the captioned disclosure.

At your request, this matter has been assigned to Shelley Fussey of this office under the supervision of David Parker. In addition, Dr. Fussey will contact you to discuss the fees on this matter. Thank you for entrusting this matter to us.

Very truly yours,

Louis T. Pirkey

cc: BethLynn Maxwell, Ph.D.
Richard Rodriguez
David Parker, Esq.

G

THE UNIVERSITY OF TEXAS
SOUTHWESTERN MEDICAL CENTER
AT DALLAS

ORIGINAL

Ray Wheatley, M.S.
Director of Technology Transfer

Office of Legal Affairs
and Technology Transfer

Shelley Fussey, Ph.D.
Arnold, White & Durkee
1900 One American Center
600 Congress Avenue
Austin, TX 78701-3248

VIA TELEFAX (512)474-7577, 1 page

Re: AUTHORIZATION TO FILE PATENT APPLICATIONS

Dear Shelley:

As we discussed, I would like to authorize the filing of two provisional patent applications consistent with our phone conference today with Dr. Thorpe. One should be directed to "coaguligand" effector molecules and the second to other molecules. I would like cost estimates for the filing of each application.

Thank you in advance for your attention to this matter. As always, if you have any questions, please contact me.

Sincerely,

Ray

Ray Wheatley

cc: Georgia Harper, J.D.
Philip Thorpe, Ph.D.

H

PATENT

UTSD:556PZ1

PROVISIONAL PATENT APPLICATION

for

CANCER TREATMENT USING THERAPEUTIC CONJUGATES THAT BIND TO AMINOPHOSPHOLIPIDS

by

Philip E. Thorpe

and

Sophia Ran

EXPRESS MAIL MAILING LABEL

NUMBER EM 545 970 247 US

DATE OF DEPOSIT July 13, 1998

I hereby certify that this paper or fee is being deposited with the United States Postal Service "EXPRESS MAIL POST OFFICE TO ADDRESSEE" service on the date indicated above and is addressed to: Assistant Commissioner for Patents, Washington D.C. 20231.

David W. Hibler

WHAT IS CLAIMED IS:

1. A method for delivering a selected therapeutic agent to intratumoral vasculature, comprising administering to an animal having a vascularized tumor a biologically effective amount of a binding ligand that comprises said selected therapeutic agent operatively attached to a targeting agent that binds to an aminophospholipid on the luminal surface of intratumoral blood vessels of the vascularized tumor.

2. The method of claim 1, wherein said targeting agent binds to phosphatidylethanolamine on the luminal surface of intratumoral blood vessels of the vascularized tumor.

3. The method of claim 1, wherein said targeting agent binds to phosphatidylserine on the luminal surface of intratumoral blood vessels of the vascularized tumor.

4. A method for killing intratumoral vascular endothelial cells, comprising administering to an animal having a vascularized tumor a biologically effective amount of a binding ligand that comprises a selected therapeutic agent operatively attached to a targeting agent that binds to an aminophospholipid on the luminal surface of intratumoral vascular endothelial cells.

5. The method of claim 4, wherein said targeting agent binds to phosphatidylethanolamine on the luminal surface of intratumoral vascular endothelial cells.

6. The method of claim 4, wherein said targeting agent binds to phosphatidylserine on the luminal surface of intratumoral vascular endothelial cells.

7. A method for inducing coagulation in intratumoral vasculature, comprising administering to an animal having a vascularized tumor a vascular endothelial cell killing amount of at least a first binding ligand that comprises a selected therapeutic agent operatively attached to a targeting agent that binds to an aminophospholipid on the luminal surface of intratumoral vasculature.

8. The method of claim 7, wherein said targeting agent binds to phosphatidylethanolamine on the luminal surface of intratumoral vasculature.

9. The method of claim 7, wherein said targeting agent binds to phosphatidylserine on the luminal surface of intratumoral vasculature.

10. A method for arresting blood flow in intratumoral vasculature, comprising administering to an animal having a vascularized tumor an amount of at least a first binding ligand effective to arrest blood flow in at least a portion of the intratumoral blood vessels, the binding ligand comprising at least a first cytotoxic or coagulative agent operatively attached to a targeting agent that binds to an aminophospholipid on the luminal surface of intratumoral blood vessels of the vascularized tumor.

11. The method of claim 10, wherein said targeting agent binds to phosphatidylethanolamine on the luminal surface of intratumoral blood vessels of the vascularized tumor.

12. The method of claim 10, wherein said targeting agent binds to phosphatidylserine on the luminal surface of intratumoral blood vessels of the vascularized tumor.

13. A method for destroying intratumoral vasculature, comprising administering to an animal having a vascularized tumor an amount of at least a first binding ligand effective to collapse or destroy at least a portion of the intratumoral blood vessels, the binding ligand comprising at least a first occluding or destructive agent operatively attached to a targeting agent that binds to an aminophospholipid on the luminal surface of intratumoral blood vessels of the vascularized tumor.

14. The method of claim 13, wherein said targeting agent binds to phosphatidylethanolamine on the luminal surface of intratumoral blood vessels of the vascularized tumor.

15. The method of claim 13, wherein said targeting agent binds to phosphatidylserine on the luminal surface of intratumoral blood vessels of the vascularized tumor.

16. A method for treating an animal having a vascularized tumor, comprising administering to said animal a therapeutically effective amount of at least a first binding ligand that comprises at least a first therapeutic agent operatively attached to a targeting agent that binds to an aminophospholipid on the luminal surface of intratumoral blood vessels of a vascularized tumor.

17. The method of claim 16, wherein said targeting agent binds to phosphatidylethanolamine on the luminal surface of intratumoral blood vessels of a vascularized tumor.

18. The method of claim 16, wherein said targeting agent binds to phosphatidylserine on the luminal surface of intratumoral blood vessels of a vascularized tumor.

19. The method of claim 16, wherein said targeting agent comprises at least a first anti-aminophospholipid antibody or antigen-binding fragment thereof.

20. The method of claim 19, wherein said targeting agent comprises at least a first human antibody or antigen-binding fragment thereof.

21. The method of claim 19, wherein said targeting agent comprises at least a first IgG or IgM antibody.

22. The method of claim 19, wherein said targeting agent comprises at least a first antigen binding region of an antibody.

23. The method of claim 19, wherein said targeting agent comprises at least a first monoclonal antibody or antigen-binding fragment thereof.

24. The method of claim 23, wherein said targeting agent comprises at least a first scFv, Fv, Fab', Fab or $F(ab')_2$ fragment of a monoclonal antibody.

25. The method of claim 23, wherein said targeting agent comprises at least a first human monoclonal antibody or antigen-binding fragment thereof.

26. The method of claim 23, wherein said targeting agent comprises at least a first humanized monoclonal antibody or antigen-binding fragment thereof.

27. The method of claim 23, wherein said targeting agent comprises at least the anti-phosphatidylserine monoclonal antibody 3SB9b, or antigen-binding fragment thereof.

28. The method of claim 23, wherein said targeting agent comprises at least a first anti-aminophospholipid monoclonal antibody, or antigen-binding fragment thereof, that is prepared by a preparative process comprising:

(a) preparing an anti-aminophospholipid antibody-producing cell; and

(b) obtaining an anti-aminophospholipid monoclonal antibody from said antibody-producing cell.

29. The method of claim 28, wherein said anti-aminophospholipid antibody-producing cell is obtained from a human patient having a disease associated with the production of anti-aminophospholipid antibodies.

30. The method of claim 28, wherein said anti-aminophospholipid antibody-producing cell is obtained by stimulating a mixed population of human peripheral blood lymphocytes with an immunogenically effective amount of an aminophospholipid sample.

31. The method of claim 28, wherein said anti-aminophospholipid antibody-producing cell is obtained by immunizing an animal with an immunogenically effective amount of an aminophospholipid sample.

32. The method of claim 31, wherein said anti-aminophospholipid antibody-producing cell is obtained by immunizing an animal via intrasplenic injection of an immunogenically effective amount of an aminophospholipid sample.

33. The method of claim 31, wherein said anti-aminophospholipid antibody-producing cell is obtained by immunizing an animal by injection of an immunogenically effective amount of a *Salmonella*-coated aminophospholipid sample or an aminophospholipid micelle sample in combination with Freund's complete adjuvant.

34. The method of claim 31, wherein said anti-aminophospholipid antibody-producing cell is obtained by immunizing a transgenic mouse that comprises a human antibody library with an immunogenically effective amount of an aminophospholipid sample.

35. The method of claim 28, wherein said preparative process comprises:

(a) fusing said anti-aminophospholipid antibody-producing cell with an immortal cell to prepare a hybridoma that produces an anti-aminophospholipid monoclonal antibody; and

(b) obtaining an anti-aminophospholipid monoclonal antibody from said hybridoma.

36. The method of claim 28, wherein said preparative process comprises:

(a) immunizing an animal with an immunogenically effective amount of an aminophospholipid sample;

(b) preparing a collection of antibody-producing hybridomas from the immunized animal;

(c) selecting from the collection a hybridoma that produces an anti-aminophospholipid antibody; and

(d) culturing the selected hybridoma to provide the anti-aminophospholipid monoclonal antibody.

37. The method of claim 36, wherein the antigen binding region of the anti-aminophospholipid monoclonal antibody is operatively attached to a human antibody framework or constant region.

38. The method of claim 36, wherein the immunized animal is a transgenic mouse that comprises a human antibody library and wherein the anti-aminophospholipid monoclonal antibody is a human monoclonal antibody.

39. The method of claim 28, wherein said preparative process comprises:

(a) obtaining the anti-aminophospholipid antibody-encoding nucleic acids from said anti-aminophospholipid antibody-producing cell; and

(b) expressing said nucleic acids to obtain a recombinant anti-aminophospholipid monoclonal antibody.

40. The method of claim 28, wherein said preparative process comprises:

(a) immunizing an animal with an immunogenically effective amount of an aminophospholipid sample;

(b) preparing a combinatorial immunoglobulin phagemid library expressing RNA isolated from the spleen of the immunized animal;

(c) selecting from the phagemid library a clone that expresses an anti-aminophospholipid antibody; and

(d) expressing the anti-aminophospholipid antibody-encoding nucleic acids from said selected clone to provide a recombinant anti-aminophospholipid monoclonal antibody.

41. The method of claim 40, wherein the immunized animal is a transgenic mouse that comprises a human antibody library and wherein the recombinant anti-aminophospholipid monoclonal antibody is a recombinant human monoclonal antibody.

42. The method of claim 16, wherein said targeting agent comprises at least a first aminophospholipid binding protein or an aminophospholipid binding fragment thereof.

43. The method of claim 42, wherein said targeting agent comprises at least a first annexin or a phosphatidylserine binding fragment thereof.

44. The method of claim 43, wherein said targeting agent comprises at least a first Annexin V or a phosphatidylserine binding fragment thereof.

45. The method of claim 42, wherein said targeting agent comprises at least a first phosphatidylethanolamine binding protein or a phosphatidylethanolamine binding fragment thereof.

46. The method of claim 45, wherein said targeting agent comprises at least a first kininogen or a phosphatidylethanolamine binding fragment thereof.

47. The method of claim 16, wherein said targeting agent comprises at least two aminophospholipid binding sites.

48. The method of claim 47, wherein said targeting agent is a dimer, trimer or multimer of an anti-aminophospholipid antibody or antigen-binding fragments thereof.

49. The method of claim 16, wherein said targeting agent is prepared by recombinant expression.

50. The method of claim 16, wherein at least a second binding ligand is administered to said animal, said second binding ligand comprising a therapeutic agent or targeting agent distinct to those of said first binding ligand.

51. The method of claim 16, wherein said binding ligand comprises at least a first anticellular therapeutic agent that kills or suppresses the growth or cell division of vascular endothelial cells.

52. The method of claim 51, wherein said binding ligand comprises at least a first steroid, cytokine, antimetabolite, anthracycline, vinca alkaloid, antibiotic, alkylating agent or epipodophyllotoxin.

53. The method of claim 51, wherein said binding ligand comprises at least a first DNA synthesis inhibitor.

54. The method of claim 53, wherein said binding ligand comprises at least a first daunorubicin, doxorubicin or adriamycin.

55. The method of claim 51, wherein said binding ligand comprises at least a first cytotoxin.

56. The method of claim 55, wherein said binding ligand comprises at least a first plant-, fungus- or bacteria-derived toxin.

57. The method of claim 56, wherein said binding ligand comprises at least a first A chain toxin, bacterial endotoxin, lipid A moiety of bacterial endotoxin, ribosome inactivating protein, α-sarcin, aspergillin, restrictocin, ribonuclease, diphtheria toxin or *Pseudomonas* exotoxin.

58. The method of claim 57, wherein said binding ligand comprises at least a first ricin A chain or deglycosylated ricin A chain.

59. The method of claim 16, wherein said binding ligand comprises at least a first coagulation factor therapeutic agent.

60. The method of claim 59, wherein said binding ligand comprises at least a first human coagulation factor.

61. The method of claim 59, wherein said binding ligand comprises at least a first vitamin K-dependent coagulation factor selected from the group consisting of Factor II/IIa, Factor VII/VIIa, Factor IX/IXa and Factor X/Xa.

62. The method of claim 59, wherein said binding ligand comprises at least a first vitamin K-dependent coagulation factor that lacks the Gla modification.

63. The method of claim 59, wherein said binding ligand comprises at least a first coagulation factor selected from the group consisting of Russell's viper venom Factor X activator, thromboxane A_2, thromboxane A_2 synthase and α2-antiplasmin.

64. The method of claim 59, wherein said binding ligand comprises at least a first Tissue Factor or Tissue Factor derivative.

65. The method of claim 64, wherein said binding ligand comprises at least a first mutant Tissue Factor deficient in the ability to activate Factor VII.

66. The method of claim 64, wherein said binding ligand comprises at least a first truncated Tissue Factor.

67. The method of claim 64, wherein said binding ligand comprises at least a first dimeric or polymeric Tissue Factor.

68. The method of claim 16, wherein said binding ligand comprises at least two therapeutic agents.

69. The method of claim 68, wherein said binding ligand comprises at least a first cytotoxic agent and at least a first coagulation factor.

70. The method of claim 68, wherein said binding ligand comprises at least two therapeutic agents operatively attached to a targeting agent comprising a single aminophospholipid binding site.

71. The method of claim 68, wherein said binding ligand comprises at least two therapeutic agents operatively attached to a targeting agent that comprises at least two aminophospholipid binding sites.

72. The method of claim 68, wherein said binding ligand comprises a targeting agent that has a plurality of aminophospholipid binding sites, and wherein a plurality of therapeutic agents are operatively attached to said targeting agent at regions distinct from said aminophospholipid binding sites.

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73. The method of claim 16, wherein said at least a first therapeutic agent is directly attached to said targeting agent.

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74. The method of claim 16, wherein said at least a first therapeutic agent is attached to said targeting agent via an antibody, or antigen binding region thereof, that binds to said therapeutic agent.

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75. The method of claim 74, wherein said binding ligand is a bispecific antibody that comprises a first, targeting antibody, or antigen binding fragment thereof, that binds to an aminophospholipid; operatively attached to a second antibody, or antigen binding fragment thereof, that binds to said at least a first therapeutic agent.

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76. The method of claim 16, wherein said targeting agent is attached by a covalent bond to said at least a first therapeutic agent or to an antibody, or antigen binding fragment thereof, that binds to said therapeutic agent.

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77. The method of claim 76, wherein said targeting agent is attached by a chemical cross-linker to said at least a first therapeutic agent or to an antibody, or antigen binding fragment thereof, that binds to said therapeutic agent.

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78. The method of claim 76, wherein said binding ligand is a fusion protein prepared by expressing a recombinant vector in a host cell, the vector comprising, in the same reading frame, a DNA segment encoding said targeting agent operatively linked to a DNA segment encoding said therapeutic agent, or an antibody, or antigen binding fragment thereof, that binds to said therapeutic agent.

79. The method of claim 16, wherein said targeting agent is attached by an avidin:biotin bridge to said at least a first therapeutic agent or to an antibody, or antigen binding fragment thereof, that binds to said therapeutic agent.

80. The method of claim 16, wherein the vasculature of said vascularized tumor is first imaged by administering to said animal a diagnostically effective amount of at least a first detectably-labeled aminophospholipid binding construct that binds to and identifies an aminophospholipid on the luminal surface of blood vessels of the vascularized tumor.

81. The method of claim 80, wherein said detectably-labeled aminophospholipid binding construct comprises a detectably-labeled anti-aminophospholipid antibody or antigen-binding fragment thereof.

82. The method of claim 80, wherein said detectably-labeled aminophospholipid binding construct comprises a detectably-labeled aminophospholipid binding protein or aminophospholipid binding fragment thereof.

83. The method of claim 80, wherein said detectably-labeled aminophospholipid binding construct comprises the X-ray detectable compound bismuth (III), gold (III), lanthanum (III) or lead (II).

84. The method of claim 80, wherein said detectably-labeled aminophospholipid binding construct comprises the radioactive ion copper^{67}, gallium^{67}, gallium^{68}, indium^{111}, indium^{113}, iodine^{123}, iodine^{125}, iodine^{131}, mercury^{197}, mercury^{203}, rhenium^{186}, rhenium^{188}, rubidium^{97}, rubidium^{103}, technetium^{99m} or yttrium^{90}.

85. The method of claim 80, wherein said detectably-labeled aminophospholipid binding construct comprises the nuclear magnetic spin-resonance isotope cobalt (II), copper (II), chromium (III), dysprosium (III), erbium (III), gadolinium (III), holmium (III), iron (II), iron (III), manganese (II), neodymium (III), nickel (II), samarium (III), terbium (III), vanadium (II) or ytterbium (III).

86. The method of claim 80, wherein said detectably-labeled aminophospholipid binding construct comprises rhodamine or fluorescein.

87. The method of claim 16, wherein an image of the tumor vasculature is first obtained by:

(a) administering to said animal a diagnostically effective amount of at least a first targeting agent-detectable agent construct that comprises a diagnostic agent operatively attached to a targeting agent that binds to an aminophospholipid on the luminal surface of blood vessels of the vascularized tumor; and

(b) detecting the targeting agent-detectable agent construct bound to an aminophospholipid on the luminal surface of tumor blood vessels, thereby obtaining an image of said tumor vasculature.

88. The method of claim 16, wherein said binding ligand is administered to said animal via intravenous administration.

89. The method of claim 16, further comprising subjecting said animal to surgery or radiotherapy.

90. The method of claim 16, further comprising administering to said animal a therapeutically effective amount of at least a first anti-cancer agent.

91. The method of claim 90, wherein said at least a first anti-cancer agent is administered to said animal simultaneously with said at least a first binding ligand.

92. The method of claim 91, wherein said at least a first anti-cancer agent and said at least a first binding ligand are administered to said animal in a single pharmaceutical composition.

93. The method of claim 90, wherein said at least a first anti-cancer agent is administered to said animal sequentially to said at least a first binding ligand.

94. The method of claim 93, wherein said at least a first anti-cancer agent is administered to said animal subsequent to the administration of said at least a first binding ligand.

95. The method of claim 90, wherein said at least a first anti-cancer agent is a chemotherapeutic agent or a radiotherapeutic agent.

96. The method of claim 90, wherein said at least a first anti-cancer agent is an anti-angiogenic agent or apoptosis-inducing agent.

97. The method of claim 90, wherein said at least a first anti-cancer agent is an antibody-therapeutic agent construct comprising an antibody, or antigen binding fragment thereof, that binds to a surface-expressed, surface-accessible or surface-localized component of a tumor cell, tumor vasculature or tumor stroma; said antibody or fragment thereof operatively linked to a therapeutic agent.

98. The method of claim 97, wherein said at least a first anti-cancer agent is an antibody-therapeutic agent construct comprising an antibody, or antigen binding fragment thereof, that binds to a cell surface antigen of a tumor cell.

99. The method of claim 98, wherein said at least a first anti-cancer agent is an antibody-therapeutic agent construct comprising an antibody, or antigen binding fragment thereof, selected from the group consisting of B3 (ATCC HB 10573), 260F9 (ATCC HB 8488), D612 (ATCC HB 9796) and KS1/4, said KS1/4 antibody obtained from a cell comprising the vector pGKC2310 (NRRL B-18356) or the vector pG2A52 (NRRL B-18357).

100. The method of claim 97, wherein said at least a first anti-cancer agent is an antibody-therapeutic agent construct comprising an antibody, or antigen binding fragment thereof, that binds to a component of tumor stroma.

101. The method of claim 100, wherein said at least a first anti-cancer agent is an antibody-therapeutic agent construct comprising an antibody, or antigen binding fragment thereof, that binds to a connective tissue component, a basement membrane component or a component of an activated platelet.

102. The method of claim 97, wherein said at least a first anti-cancer agent is an antibody-therapeutic agent construct comprising an antibody, or antigen binding fragment thereof, that binds to a surface-expressed, surface-accessible or surface-localized component of intratumoral blood vessels of a vascularized tumor.

103. The method of claim 102, wherein said at least a first anti-cancer agent is an antibody-therapeutic agent construct comprising an antibody, or antigen binding fragment thereof, that binds to a surface-expressed component of intratumoral blood vessels of a vascularized tumor.

104. The method of claim 103, wherein said at least a first anti-cancer agent is an antibody-therapeutic agent construct comprising an antibody, or antigen binding fragment thereof, that binds to an intratumoral vasculature cell surface receptor.

105. The method of claim 104, wherein said at least a first anti-cancer agent is an antibody-therapeutic agent construct comprising an antibody, or antigen binding fragment thereof, that binds to endoglin, a TGFβ receptor, E-selectin, P-selectin, VCAM-1, ICAM-1, PSMA, a

VEGF/VPF receptor, an FGF receptor, a TIE, $\alpha_v\beta_3$ integrin, pleiotropin, endosialin or an MHC Class II protein.

106. The method of claim 105, wherein said at least a first anti-cancer agent is an antibody-therapeutic agent construct comprising an antibody, or antigen binding fragment thereof, that binds to endoglin, E-selectin or VCAM-1.

107. The method of claim 102, wherein said at least a first anti-cancer agent is an antibody-therapeutic agent construct comprising an antibody, or antigen binding fragment thereof, that binds to a ligand or growth factor that binds to an intratumoral vasculature cell surface receptor.

108. The method of claim 107, wherein said at least a first anti-cancer agent is an antibody-therapeutic agent construct comprising an antibody, or antigen binding fragment thereof, that binds to VEGF/VPF, FGF, TGFβ, a ligand that binds to a TIE, a tumor-associated fibronectin isoform, scatter factor/hepatocyte growth factor (HGF), platelet factor 4 (PF4), PDGF or TIMP.

109. The method of claim 102, wherein said at least a first anti-cancer agent is an antibody-therapeutic agent construct comprising an antibody, or antigen binding fragment thereof, that binds to a ligand:receptor complex or a growth factor:receptor complex, but that does not bind to the ligand or growth factor, or to the receptor, when the ligand or growth factor or the receptor is not in the ligand:receptor or growth factor:receptor complex.

110. The method of claim 102, wherein said at least a first anti-cancer agent is an antibody-therapeutic agent construct comprising an antibody or antigen binding fragment thereof, that binds to a cytokine-inducible component of intratumoral blood vessels of a vascularized tumor.

111. The method of claim 102, wherein said at least a first anti-cancer agent is an antibody-therapeutic agent construct comprising an antibody or antigen binding fragment thereof, that binds to a coagulant-inducible component of intratumoral blood vessels of a vascularized tumor.

112. The method of claim 97, wherein said at least a first anti-cancer agent is an antibody-therapeutic agent construct comprising an anti-tumor cell, anti-tumor vasculature or anti-tumor stroma antibody, or antigen binding fragment thereof, operatively linked to a cytotoxic agent.

113. The method of claim 97, wherein said at least a first anti-cancer agent is an antibody-therapeutic agent construct comprising an anti-tumor cell, anti-tumor vasculature or anti-tumor stroma antibody, or antigen binding fragment thereof, operatively linked to a coagulation factor or an antibody, or antigen binding fragment thereof, that binds to a coagulation factor.

114. The method of claim 16, wherein said animal has a vascularized tumor of at least about medium size.

115. The method of claim 114, wherein said animal has a large vascularized tumor.

116. The method of claim 16, wherein said animal is a mouse.

117. The method of claim 16, wherein said animal is a human patient.

118. A method for treating an animal having a vascularized tumor, comprising administering to said animal at least a first pharmaceutical composition comprising an amount of at least a first binding ligand effective to specifically kill at least a portion of the intratumoral vascular endothelial cells; wherein said binding ligand comprises at least a first cytotoxic agent operatively attached to a targeting agent that binds to an aminophospholipid expressed on the luminal surface of intratumoral blood vessels of the vascularized tumor.

119. A method for treating an animal having a vascularized tumor, comprising administering to said animal at least a first pharmaceutical composition comprising an amount of at least a first binding ligand effective to promote blood coagulation specifically in the intratumoral vasculature, the binding ligand comprising at least a first cytotoxic or coagulative agent operatively attached to a targeting agent that binds to an aminophospholipid expressed on the luminal surface of intratumoral blood vessels of the vascularized tumor.

120. A method for treating an animal having a vascularized tumor, comprising administering to said animal at least a first pharmaceutical composition comprising an amount of at least a first binding ligand effective to cause specific destruction of the intratumoral vasculature, the binding ligand comprising at least a first occluding or destructive agent operatively attached to a targeting agent that binds to an aminophospholipid expressed on the luminal surface of intratumoral blood vessels of the vascularized tumor.

121. A method for treating cancer, comprising administering to an animal with a vascularized tumor at least a first pharmaceutical composition comprising an amount of at least a first binding ligand effective to induce tumor necrosis, the binding ligand comprising at least a first therapeutic agent operatively attached to a targeting agent that binds to an aminophospholipid expressed on the luminal surface of intratumoral blood vessels of the vascularized tumor.

122. The method of any one of claims 118 to 121, wherein said targeting agent binds to phosphatidylethanolamine expressed on the luminal surface of intratumoral blood vessels of the vascularized tumor.

123. The method of any one of claims 118 to 121, wherein said targeting agent binds to phosphatidylserine expressed on the luminal surface of intratumoral blood vessels of the vascularized tumor.

124. A method for treating a patient with cancer, comprising selecting a suitable patient having a vascularized tumor and administering to said patient a therapeutically effective amount of at least a first pharmaceutical composition comprising at least a first binding ligand that comprises at least a first therapeutic agent operatively attached to a targeting agent, said targeting agent binding to an aminophospholipid expressed on the luminal surface of intratumoral blood vessels of the vascularized tumor.

125. A method for treating cancer, comprising:

(a) forming an image of a vascularized tumor by administering to an animal having a vascularized tumor a diagnostically minimal amount of at least a first targeting agent-detectable agent construct that comprises a detectable agent operatively attached to a targeting agent that binds to an aminophospholipid on the luminal surface of blood vessels of the vascularized tumor, thereby forming a detectable image of the tumor vasculature; and

(b) subsequently administering to said animal a therapeutically optimized amount of at least a first targeting agent-therapeutic agent construct comprising a therapeutic agent operatively attached to a targeting agent that binds to an aminophospholipid

on the tumor blood vessel luminal surface and thereby destroys the tumor vasculature.

126. A method for treating an animal having a vascularized tumor, comprising administering to said animal a therapeutically effective amount of a pharmaceutical composition comprising at least a first construct comprising an anti-aminophospholipid antibody, or antigen binding fragment thereof, directly or indirectly linked to at least a first therapeutic agent.

127. A method for treating an animal having a vascularized tumor, comprising administering to said animal a therapeutically effective amount of a pharmaceutical composition comprising an aminophospholipid binding protein directly or indirectly linked to at least a first therapeutic agent.

128. A method for treating an animal having a vascularized tumor, comprising administering to said animal a therapeutically effective amount of a pharmaceutical composition comprising Annexin V directly or indirectly linked to at least a first therapeutic agent.

129. A binding ligand comprising a targeting agent that binds to an aminophospholipid operatively attached to at least a first cytotoxin or coagulant.

130. The binding ligand of claim 129, wherein said targeting agent binds to phosphatidylethanolamine.

131. The binding ligand of claim 129, wherein said targeting agent binds to phosphatidylserine.

132. The binding ligand of claim 129, wherein said targeting agent comprises at least a first anti-aminophospholipid antibody or antigen-binding fragment thereof.

133. The binding ligand of claim 132, wherein said targeting agent comprises at least a first human, humanized or monoclonal antibody or antigen-binding fragment thereof.

134. The binding ligand of claim 129, wherein said targeting agent comprises at least a first aminophospholipid binding protein or an aminophospholipid binding fragment thereof.

135. The binding ligand of claim 134, wherein said targeting agent comprises at least a first annexin or a phosphatidylserine binding fragment thereof.

136. The binding ligand of claim 134, wherein said targeting agent comprises at least a first phosphatidylethanolamine binding protein, kininogen or a phosphatidylethanolamine binding fragment thereof.

137. The binding ligand of claim 129, wherein said binding ligand comprises at least a first cytotoxin.

138. The binding ligand of claim 129, wherein said binding ligand comprises at least a first coagulant.

139. The binding ligand of claim 138, wherein said binding ligand comprises at least a first Tissue Factor or Tissue Factor derivative.

140. The binding ligand of claim 129, wherein said at least a first cytotoxin or coagulant is directly attached to said targeting agent.

141. The binding ligand of claim 129, wherein said at least a first cytotoxin or coagulant is indirectly attached to said targeting agent via an antibody, or antigen binding region thereof, that binds to said cytotoxin or coagulant.

142. The binding ligand of claim 129, dispersed in a pharmaceutically acceptable formulation.

143. A bispecific antibody, comprising a first antigen-binding region that binds to an aminophospholipid operatively attached to a second antigen-binding region that binds to a therapeutic agent.

144. The bispecific antibody of claim 143, comprising a first antigen-binding region that binds to phosphatidylethanolamine.

145. The bispecific antibody of claim 143, comprising a first antigen-binding region that binds to phosphatidylserine.

146. The bispecific antibody of claim 143, comprising a first antigen-binding region that binds to an aminophospholipid operatively attached to a second antigen-binding region that binds to Tissue Factor or a Tissue Factor derivative.

147. The bispecific antibody of claim 146, further comprising Tissue Factor or a Tissue Factor derivative bound to said second antigen-binding region.

148. A construct comprising an aminophospholipid binding protein, or aminophospholipid binding fragment thereof, operatively attached to a cytotoxin or coagulant.

149. An annexin conjugate, comprising Annexin V operatively attached to truncated Tissue Factor.

150. A medicament, comprising:

(a) a first pharmaceutical composition comprising a diagnostically effective amount of a targeting agent-detectable agent construct that comprises a detectable agent operatively attached to a first targeting agent that binds to an aminophospholipid; and

(b) a second pharmaceutical composition comprising a therapeutically effective amount of a targeting agent-therapeutic agent construct that comprises a

therapeutic agent operatively attached to a second targeting agent that binds to an aminophospholipid.

151. The medicament of claim 150, wherein said first or second targeting agents are anti-aminophospholipid antibodies or antigen-binding fragments thereof.

152. The medicament of claim 150, wherein said first or second targeting agents are aminophospholipid binding proteins or aminophospholipid binding fragments thereof.

153. The medicament of claim 150, wherein said first and second targeting agents are anti-aminophospholipid antibodies, or fragments thereof, obtained from the same antibody preparation or antibody-producing hybridoma.

154. The medicament of claim 150, further comprising an anti-cancer agent.

155. A kit comprising, in at least a first suitable container, a biologically effective amount of a first anti-cancer agent comprising a first targeting agent that binds to an aminophospholipid operatively attached to at least a first therapeutic agent; and a biologically effective amount of at least a second anti-cancer agent.

156. The kit of claim 155, wherein said at least a second anti-cancer agent is a chemotherapeutic agent, radiotherapeutic agent, anti-angiogenic agent or apoptosis-inducing agent.

157. The kit of claim 155, wherein said at least a second anti-cancer agent is an antibody construct comprising an antibody, or antigen binding fragment thereof, that binds to a surface-expressed, surface-accessible or surface-localized component of a tumor cell, tumor vasculature or tumor stroma; said antibody or fragment thereof operatively linked to a therapeutic agent.

158. The kit of claim 155, wherein said first and second anti-cancer agents are comprised within a single container.

159. The kit of claim 155, wherein said first and second anti-cancer agents are comprised within distinct containers.

160. A therapeutic cocktail, comprising a combined effective amount of a first anti-cancer agent and at least a second anti-cancer agent comprising a targeting agent that binds to an aminophospholipid operatively attached to at least a first therapeutic agent.

ABSTRACT

Disclosed is the surprising discovery that aminophospholipids, such as phosphatidylserine and phosphatidylethanolamine, are specific, accessible markers of the luminal surface of tumor blood vessels. The present invention thus provides targeted therapeutic conjugates and constructs that bind to aminophospholipids, and methods of specifically delivering toxins and coagulants to the aminophospholipids of tumor blood vessels, thereby inducing thrombosis and tumor regression.